

BIOLOGICAL CURVES OBTAINED DURING THE ONSET AND COURSE OF TUBERCULOUS INFECTION

BY ALFRED CAULFEILD, M.B., AND F. S. MINNS, M.B.

CHICAGO, ILL., 1911.

IN 1911 one of us published preliminary reports* upon the effect of certain tuberculous sera upon tuberculo-antigen. This effect was estimated by the lessened adsorption that antigen-serum mixtures had for complement in contrast to that of the corresponding antigen-salt mixtures. This phenomenon is exactly the reverse of complement fixation, and although the technic is an adaptation of the latter, the protocol necessary for the routine demonstration of this reverse phenomenon differs from the necessary arrangement for complement fixation.

As the purpose of this paper is to demonstrate the relation between the clinical progress and biological curves obtained by the repetition of these test-tube reactions, together with repeated quantitative estimations of the tuberculin sensitiveness, we do not propose to deal extensively with the technic of the methods, which have been fairly fully outlined in the former publications. The technic therein given is essentially the basis of the present report, although various modifications have been adopted to increase the delicacy and accuracy of the test. One important detail of the technic might, however, be mentioned, and that is the necessity of estimating the natural hemolytic strength of the serum to the corpuscles of whatever system used. In the former reports this factor was controlled rather than eliminated. Subsequently we found it consumed less time and gave greater accuracy to first absorb the natural hemolysin by incubation of the inactivated sera with washed sheep-corpuscles.

As we have found it necessary, for convenience of expression, to introduce two terms descriptive of the end-results of the test-tube reactions, a brief discussion of the nomenclature at this point may facilitate the subsequent use of these terms.

The technic adopted to demonstrate this reverse phenomenon to complement fixation is based upon the fact that all antigens are capable of non-specifically adsorbing complement in various degrees. Now, if to an appropriate series of antigen dilutions, whose complement-adsorbing capacities are quantitatively shown, sera are added, it will be found that certain sera give—(1) true complement fixation (the demonstration of this taking place in appropriate antigen dilutions where only minimal parts of a unit of complement

* Caulfeild: "Investigations on Pulmonary Tuberculosis," *Jour. Med. Research*, January, 1911, p. 128; Caulfeild: "Correlation of Clinical Progress with The Results of Immunological Studies," *Arch. Int. Medicine*, October, 1911, vol. viii, p. 440.

are adsorbed; (2) others will show no effect (indifferent reaction); (3) others will so react with the antigen that these antigen-serum mixtures show great loss of complement-adsorbing power (inhibitive reaction). Experiments have been given regarding the specificity of this latter, and will be enlarged upon in a later publication.

Taking the phenomena in the reverse order, the following remarks may help to explain the method adopted to record graphically the end-results:

1. *Inhibitive Phenomenon*.—These sera so digest or react with the antigen* that, in contrast to the antigen-salt mixtures, the corresponding antigen-serum mixtures show a loss of capacity for complement adsorption. Different sera show this phenomenon in different degrees, and the protocol experiment is arranged to demonstrate this quantitatively. For convenience of expression the phenomenon has been termed the inhibitive reaction, in contrast to complement fixation. In reality it is the inhibiting effect on what was formerly, before the addition of serum, the power of that amount of antigen in the same degree of dilution to non-specifically adsorb complement—estimated qualitatively. The protocols are arranged so as to show this power in three degrees: Where the amount of antigen-adsorbing power equals four units of complement the inhibitive reaction would be called complete if the corresponding antigen-serum mixture showed an adsorption of not more than one unit of complement, i. e., complete hemolysis, and the potentiality of releasing three units. In the nomenclature adopted in the curves this is I_1 ; if the antigen-serum mixture showed an adsorption potentiality of two units, I_2 , and of three units, I_3 .

2. *The Indifferent Reaction*.—These sera react in no way with the antigen, that is, if the capacity of each serum to non-specifically adsorb complement be estimated and considered in the results obtained in the antigen-serum mixtures it will be seen that the effect upon complement is the same as in the corresponding antigen-salt mixtures. In other words, neither the reaction of fixation nor the inhibitive reaction is given.

3. *True Fixation of Complement*.—Only those sera which show no hemolysis in the tubes where the antigen dilutions are capable of adsorbing only a minimal part of a unit of complement are accepted as positive. In the plotted curves what would be ordinarily called a + + + reaction is termed Fixation 1, to correspond with the terminology used for the inhibitive phenomenon.

The estimation of the tuberculin sensitiveness (or hypersensitiveness) has been made by the von Pirquet cutaneous method, with the technic described in a former publication,† except latterly, when for a time both the cutaneous and the intracutaneous method of Mantoux have been used. The amount of tuberculin has been, with the former, 10 c.mm. of a 50 per cent. solution of O. T., and the degree of sensitiveness judged from the extent of the reaction. In selected cases it has been possible to take readings every day. This method has given us more satisfaction than a determination of the minimal reacting

* Attention should be drawn to the fact that this particular antigen is an alcohol-ether extract of tubercle bacilli, and that true complement fixation is obtained with it in only a very small percentage of cases. This low percentage is in very marked contrast to that obtained with most other tuberculo-antigens. These percentages are outlined in Table 1. (See p. 3.)

† Jour. Med. Research, vol. xxiv, No. 1, p. 103, 1911.

dose, inasmuch as it seems as accurate, gives a greater amplitude in the results, and requires only one application in contrast to the two or more necessary to gauge exactly the minimal dose which will give a reaction. For the same reason we are now using a $\frac{1}{10}$ mg. O. T. in 20 c.mm. for the intradermal test, and gauging the degree of sensitiveness by the extent of the reaction.

The earlier reports were based upon part of the investigation carried out on the sanatorium cases shown in Table 1. Owing to the increased scope afforded by the Tuberculosis Clinic of the Toronto General Hospital, the work has again been taken up, and now represents observations upon a much greater number than that outlined in Table 1, which was compiled at a time when it was convenient finally to sum up the cases investigated up to that particular date. We feel that the additional observations would make no material change in the percentage results.

TABLE 1

NUMBER OF CASES	WHERE OBTAINED	NUMBER OF TESTS WITH ALCOHOL-ETHER EXTRACT	NUMBER OF TESTS WITH OTHER TUBERCULO-ANTIGENS
154	In sanatorium.....	322	42
204	In Out-door Department. General Hospital.....	282	34
	Total.....	604	76

Of this number, 101 cases had had an average of 3.4 tests with alcohol-ether antigen.

True complement fixation was obtained in:	Sanatorium cases in:	34 per cent. cases with other antigens.
True complement fixation was obtained in:	Outdoor Department, General Hospital:	35 per cent. cases with other antigens.
True complement fixation was obtained in:	Sanatorium cases:	7.6 per cent. cases with alcohol-ether antigen.
True complement fixation was obtained in:	Outdoor Department:	4.8 per cent. cases with alcohol-ether antigen.
Full inhibitive reaction:	Sanatorium cases:	22.4 per cent. cases with alcohol-ether antigen.
Full inhibitive reaction:	Outdoor Department:	29.4 per cent. cases with alcohol-ether antigen.

The above results are compiled from data on cases which were investigated while they were resident in sanatoria, and upon whom in general no further observation has been possible. The remaining cases are those investigated in a routine fashion at the Tuberculosis Clinic of the Toronto General Hospital up to March 15, 1914, as this date was a convenient one to take for a review of the cases from both a clinical and a bacteriological point of view. The work, however, has been carried on from that time, and explains in a few of the charts additional data obtained after March 15th.

As well as the observations upon human beings, considerable work has been done with cows and rabbits experimentally injected with different strains of acid-fast bacilli. In only one instance out of about 40 rabbits has the inhibitive reaction been obtained. This occurred in one rabbit which successfully withstood the inoculation of 1,400,000,000 of living bacilli. This strain was obtained from an abscess following a Friedmann inoculation. True fixation can

be obtained in rabbits* with the alcohol-ether antigen as well as with other tuberculo-antigens. In contrast to the results in small laboratory animals, the reaction has been observed in all degrees in cows. Work is at present under way with these animals to correlate these findings with other data.

As it would be impossible in this report to deal with the material that has accumulated in these investigations by analyzing each case, although it is by this method, as well as by subsequent groupings, that we have come to the conclusions we now hold, our purpose will best be fulfilled, it would seem, by presenting the results under various groupings, and by further illustrating the various points by charting the results obtained in particular cases.

A. Results Obtained in Clinical Normals.—In the beginning of these investigations samples of blood from clinical normals were used for the purpose of "controls." However, as the application of the tests developed, and as variations both in the test-tube results and the clinical life of certain of the controls were obtained, the conception was formed that from just such material data might be obtained which would throw light upon "immunity to tuberculosis." No doubt this hope originated in the deductions drawn from the results of tuberculin tests on healthy subjects and postmortem statistics regarding the prevalence of the lesions of healed tuberculosis. These allow one to believe that during the life of different individuals exposures to tubercle bacilli and bacillary implantations take place, and that, in those remaining clinically free from tuberculosis, the implantations are successfully resisted within varying periods of time and varying degrees of biological reaction and anatomical involvement. Our belief is that we obtain immunity to tuberculosis (by which is meant definitely established clinical tuberculosis) through exposures or implantations less in amount or virulence than our resistance, and that our resistance or immunity is fostered by these successfully resisted implantations. Whether we regard reinfection to be caused from within or without is not material to the point at issue.

Thus it has seemed to us that if these biological results can be of value (as they seem to be) in the definitely tuberculous, they should, if carried out continuously upon a sufficient number of clinical normals, throw some light upon the problem of immunity. In this way only would it seem possible in humans to contrast the reactions existent before, during, and after successfully resisted implantation. The contrast to this in the reactions following various degrees of early clinical infection is, of course, easily obtained. The value one will attach to the results in this connection will depend upon each observer's belief in the possibility of the tests representing a biological state (or physical condition depending on a biological state) and their specificity.

The list as it at present stands in the class of clinical normals is perhaps far from ideal, but a number of difficulties have arisen that were unforeseen in the beginning. The work was interrupted for about a year, and again observations were begun on individuals, who for various reasons were not again available for further tests. As would be expected, the most consistent series of observations has been obtained upon physicians, their friends, and medical students.

Table 2 gives the total number of cases included in this list, grouped under

* Caulfeild: Proc. Royal Society, B. vol. lxxxiv, p. 390, 1911.

the year of the initial observation and the biological classification. It is noticeable that with increase of the inhibitive phenomenon there is roughly an increase in the tuberculin sensitiveness. Four cases have shown variations which we consider outside the error of the technic. Of these, No. 4 developed clinical tuberculosis. The lesion was a slight one of the right apex, and appeared to be an activation of a former infection. The diagnosis was agreed to by an independent worker in tuberculosis, who had no knowledge of the laboratory findings. This case, a laboratory "Diener," made excellent progress without entirely giving up his work at any time. He was alive and well and performing manual labor in 1913. Case No. 17 is the only one of the four showing variations whose findings are not charted in Fig. 1. This was not done because sufficient time had not elapsed for more than two closely spaced blood examinations. Case No. 14, the only instance of a full inhibitive phenomenon not subsequently giving a variation, is a physician who is spending most of his time in tuberculosis work; his second blood test was between I₁ and I₂.

TABLE 2

YEAR OF FIRST OBSERVATION	NO. OF CASE	RESULT OF FIRST TEST-TUBE REACTION				TUBERCULIN SENSITIVENESS
		I ₁	I ₂	I ₃	IND.	
1910-11.....	1	..	..	..	+	16 x 16 mm.
1910-11.....	2	+(V.)	..	..	..	Variations marked.
1910-11.....	3	..	+	..	..	Slight variations.
1910-11.....	4	..	..	..	+(V.)	25 x 30.
1913.....	5	..	..	+	..	12 x 12.
1913.....	6	..	..	..	+	Negative.
1913.....	7	..	..	..	+	Negative.
1913.....	8	..	..	..	+	10 x 12.
1913.....	9	..	..	+	..	15 x 18.
1913.....	10	..	..	..	+	Negative.
1913.....	11	..	..	..	+	Negative. (?)
1913.....	12	..	+(V.)	..	..	Variations.
1913.....	13	..	..	+	..	12 x 12. (?)
1913.....	14	+	..	..	..	25 x 25.
1913.....	15	..	..	..	+	10 x 15.
1913.....	16	..	..	..	+	15 x 15.
1914.....	17	..	+(V.)	..	..	10 x 12. (25 x 40)
1914.....	18	..	..	..	+	Negative.
Totals...	..	2	3	3	10	

Up to the present the total number of observations made on the above is 53.

The letter V. means that subsequent tests showed a variation of more than one degree of the nomenclature (a variation of one degree only being considered within the range of experimental error). Four cases, including the one case of positive clinical tuberculosis, have shown variations, *i. e.*, 22 per cent. Case No. 2 developed tuberculosis during the observations. Case No. 17, a research worker, has shown slight variations gave complement fixation with a bacillus emulsion antigen, and a general febrile reaction of 101° with 0.2 mg. O. T. given subcutaneously.

In Fig. 1 an example is given (Case No. 1) of repeatedly similar results. Case No. 3, a physician working in tuberculosis, has only had two blood tests, but as far as they are concerned the variation is considered as easily due to the possible error of the technic or interpretation. The rough correlation that seems to exist between a high inhibitive reaction and marked tuberculin sensitiveness is well shown. Case No. 2, already previously reported in 1911, was suspected of clinical tuberculosis, although the actual clinical demonstration was lacking. In this case a very marked change in the character of the cutaneous reaction was noticeable between the second and third tests. The maximum intensity was reached on the fourth day in the second test, and on the beginning of the second day in the third test; the fourth test was also more rapid in its onset than the second.

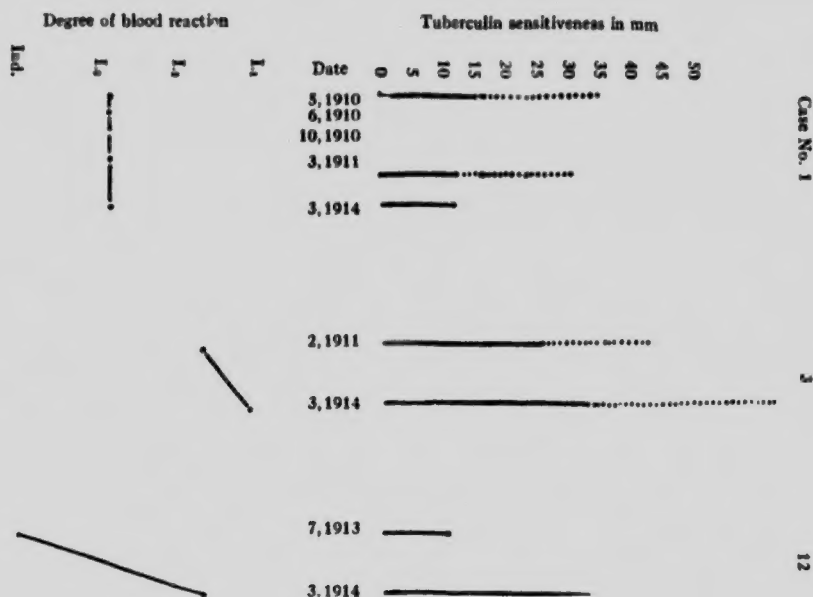


FIG. 1

The date shows only the month and the year: the spacing is only approximate to avoid unwieldiness.

The dotted lines of the tuberculin reaction signify that amount of halo around the infiltration.

The significance of the rapid onset of the day of maximum intensity of this reaction is referred to in the discussion of these cases.

Case No. 12 remarked before the second blood test that he had been slightly troubled with his knee; a clinical examination revealed no evidence of any

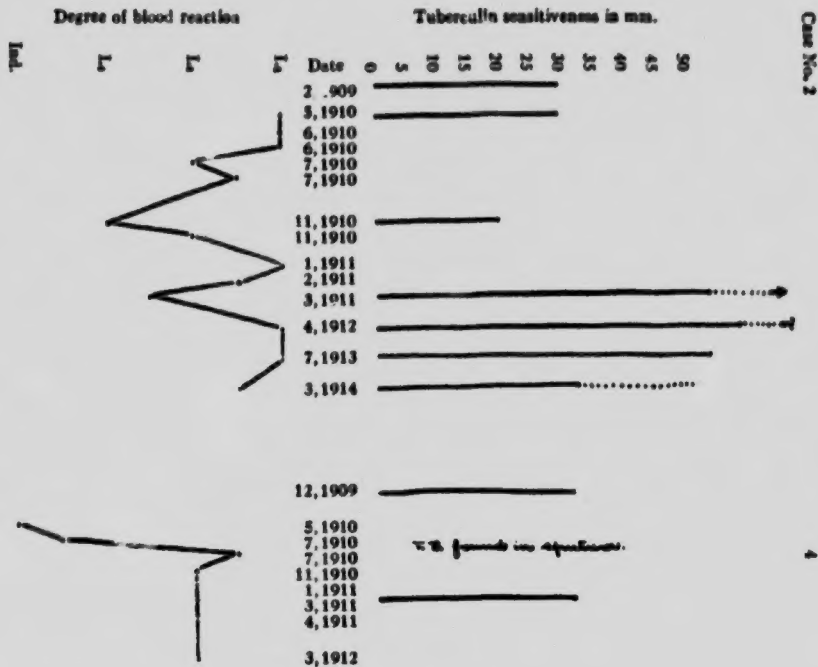


FIG. 1 (Continued)

character, however. The tuberculin test was performed a week or so later. It should be remarked here that there is no possible chance of a bias on the part of the one who reads the end-results. All samples of blood are inactivated, have their hemolysin extracted, and are put up under a number.

The reason why the cases giving variations have had relatively more observations made on them is because once a variation is obtained much more endeavor is made to get a repetition. Further, as this represents work continued over a long period of time, it has very frequently been impossible to get these cases when desired.

B. Results Obtained in Cases of Definite Exposure.—This class is very small in number, because we have included in it only cases for whom the exposure has been very definite, and where there was no evidence whatever of a clinical manifestation of tuberculosis. It does not include the cases which in a routine manner are collected in a tuberculosis clinic when any one in the household is found to have contracted tuberculosis. Sufficient time has not elapsed to allow us to check this material, for whom the exposure generally is still

continuing. Further, no case fulfilling the conditions outlined has been included until a sufficient period of time has successfully elapsed, so that one is as certain as possible that clinical tuberculosis has not resulted.

Table 3 shows the blood reactions of these few cases, together with the amount of the tuberculin sensitiveness. Three cases coming in the I.₁ column show practically negative results. In Case 2 this is easily explained by the duration since the exposure. In Cases 5 and 7 this cannot be the explanation. We feel that it is, however, probably due to the long duration of the exposure. This was the explanation offered by one of us* in 1911 for the rarely found negative tuberculin tests obtained in undoubted cases with a slight involvement and good prognosis.

TABLE 3

No. OF CASE	I. ₁	I. ₂	I. ₃	NOTES REGARDING THE DURATION OF THE EXPOSURES, AND TIME SINCE EXPOSURE THAT BLOOD WAS EXAMINED.
1	20 x 30	..	..	Exposed for about a year; about six months after the exposure.
2	5 x 5	..	..	Exposed for about a year; fourteen months after the exposure.
3	..	30 x 30	..	Exposed on and off for two and a half years; about three months after exposure.
4	{ 15 x 15 25 x 30 }	..	..	(See note below)
5	5 x 5	..	..	Exposed for many years; one month after exposure.
6	..	30 x 40	..	Exposed for about six months; six months after exposure.
7	10 x 10	..	..	Exposed for many years; six months after exposure.

The numbers represent the millimeter measurements of the cutaneous test. Case 4 gave a remarkably clear-cut result, aged twenty-two, had been intimately exposed to one of the opposite sex; previously not likely to have had any exposure. About one month afterward patient sought medical advice, not because of any complaint, but because he only then learnt that he had been exposed to tuberculosis. The cutaneous test at that time (June, 1913) measured 15 x 15 mm.; in August a full inhibitive reaction was obtained, and in November, 1913, the cutaneous test measured 25 x 30 mm.

While we feel that seven cases are not sufficient from which to draw conclusions, still the contrast between the high degree of the inhibitive phenomenon found in all the exposed cases is in marked contrast to that obtained in the clinical normal group. This is even more marked if one excludes from the clinical normal group those who showed no variation in the blood or tuber-

* Caulfeild and Beatty: Jour. of Med. Research, 1911, vol. xxiv, No. 1, pp. 110 and 116.

culin tests, or who were exposed to tuberculosis, as were the physicians working extensively with that disease.

Thus if one excludes from the clinical normal group those whose blood and tuberculin tests showed variations, those physicians whose work brought them in constant contact with cases, and the one case in which tuberculosis developed, it leaves all the remaining examples in the I_3 or indifferent class. Also it leaves all the undoubtedly exposed cases and those doubtful clinical normals at one time or another in the two higher grades of the inhibitive phenomenon. In other words, the two tests make it possible to take from the clinical normal class certain ones which give the same findings as the undoubtedly exposed cases, which still are free from clinical tuberculosis. That is, these clinical normals were exposed and received their tubercle bacilli implantations.

C. Results Obtained in Cases Giving Doubtful Evidence of Pulmonary Tuberculosis.—It is perhaps as well here to make some observations regarding the clinical classifications adopted, under which the results of the biological findings are shown. It is always a difficult thing—if not impossible—to divide patients into tuberculous and non-tuberculous groups, and this is especially true in a busy tuberculosis clinic of a general hospital. On the staff of such a clinic there naturally must be differences in skill and expertness in technic and interpretation. In view of these conditions it was felt by us that it would perhaps be easier and less influenced by subjective error to form this list (Table 4) by excluding those cases, whom the one or two physicians who examined the patients felt without doubt were cases of tuberculosis; and by further excluding those cases which had already been discharged from the clinic as non-tuberculous. These restrictions probably resulted in the inclusion of a greater percentage of the tuberculosis free than would otherwise have resulted had further subdivision been adopted. It is often easier to make a diagnosis than to exclude the possibility. The only laboratory result playing a part in the classification was the sputum report. These cases then might be summed up by the statement that they included those in whom it was possible that other pathologic conditions might explain the symptoms and findings, or were those whom it seemed advisable to keep under observation because tuberculosis at the moment could not be excluded.

On these cases, the tests have usually been of value only when their repetition showed variations, and the variation, if sufficiently marked, corresponded with the clinical course. This involves naturally a very careful consideration and review of each case. Now, as deductions drawn by any particular interpreter must to a certain extent be biased, the proof of the correctness of the basis of the interpretation must rest upon a large number of cases. It would be impossible in this communication to detail a sufficient number of cases to meet this just criticism, nor do we feel that at present sufficient material has been worked over. Such cases as these in tuberculosis often require many months to furnish the proof of the correctness of the diagnosis. No more than one or two examples will be given to indicate the basis of the interpretation.

The following cases illustrate the aid afforded by the reactions. They are all, as already outlined, cases in whom the diagnosis could not positively be

made, nor could tuberculosis be excluded. The classification, of course, is based upon a consideration of both the physical findings and the history.

(1) Hospital No. 1433. The blood reaction on December 11, 1913, was I.₂, at which time the cutaneous test measured 15 x 15 mm. On April 1, 1914, both reactions were the same, but in the meantime the patient had lost the suggestive symptoms. Our conclusion was that some other pathologic condition explained the clinical complex found at the time the patient first presented himself.

(2) Hospital No. 782. The blood reaction on December 20, 1913, was I.₂, and the cutaneous test measured 30 x 30 mm. On April 1, 1914, the blood reaction was found to be the same, and although the cutaneous test was overlooked, the clinical improvement enabled us to support the diagnosis in the same manner as in the preceding case.

(3) Hospital No. 4124. Between August, 1913, and March, 1914, four blood tests were made. All varied between I.₁ and I.₂. Slight variations were obtained in the cutaneous tests. The clinical picture remained stationary or slightly worse. The diagnosis was made of positive tuberculosis. Incidentally, in support of this, a positive complement fixation with other tuberculo-antigens and a negative Wassermann were obtained.

(4) Hospital No. 4122. Three blood tests were made between August, 1913, and May, 1914, and two cutaneous tests. The blood results were as follows: Ind. I.₁, I.₂. The cutaneous tests were 5 x 5 mm. and 25 x 30 mm. Marked clinical improvement took place during this period. This strengthened the opinion that the patient had been suffering from tuberculosis.

(5) From August, 1913, to March, 1914, three blood tests were made, with the following results: Fixation, Ind. and I.₂. Clinically increased well-being helped a positive diagnosis. In this case only one cutaneous test was performed. The clinical picture included enlarged abdominal glands (?), and needed an exclusion of new-growths.

Of these five examples, it can be said that the first two cases gave results which might be duplicated among the clinical normals (see Table 2 and Fig. 1); that Case 4 is very similar to the exposed Case No. 4 in Table 3 and Fig. 1, and that the results, both biological and clinical, in Cases 3 and 5, are frequently encountered among the definitely tuberculous (Fig. 2).

It so happens that one of us has comparable data (Table 4) obtained on 30 cases resident in sanatoria. In but few of these did the writer take any part in the clinical classification. Many of the cases had been resident in the sanatoria for long periods of time, and had experienced the benefit of the change from their former life to the better conditions existing in the sanatoria. Most of the patients were at a free sanatorium, and as such represent a weeding-out of the cases of tuberculosis clinics in the cities. Further, if such cases were regarded as doubtful after a period of time in a sanatorium, they were likely to be those who had the power to improve fairly rapidly when given a better chance than that afforded by former circumstances. There is, of course, the

possibility that some of them were tuberculosis free and got their exposure in the sanatorium, thus explaining the biological reactions. The contrast between the two sets of results is marked.

TABLE 4

DATA OBTAINED FROM TUBERCULOSIS CLINIC IN GENERAL HOSPITAL						DATA OBTAINED ON CASES IN SANATORIA				
No. of Case	I ₁	I ₂	I ₃	Ind.	Fixa- tion	No. of Case	I ₁	I ₂	I ₃	Ind.
1		18.22	..	..	..	1	..	—	..	..
r 2	20.25	..	..	..	..	2	..	..	8.10	..
3	..	Neg.	..	..	..	r 3	25.30 (50.50)	..	..	..
4	..	..	10.10	..	..	4	..	..	—	..
5	10.18	..	..	..	..	5	30.40	..	..	..
6	..	..	Neg.	..	..	6	..	..	..	12.15
7	10.10	..	..	..	..	7	..	..	15.15	..
8	..	18.18	..	..	..	8	30.30 (50.50)	..	..	..
r 9	25.30	..	..	..	..	9	18.18	..	..	..
10	Neg.	..	..	..	..	10	35.35	..	..	..
11	..	10.10	..	..	..	11	22.25	..	..	..
r 12	..	..	..	..	..	12	..	..	..	..
r 13	15.35	..	..	..	..	13	..	Neg.	..	..
14	10.10	..	..	..	..	14	..	18.20	..	..
r 15	..	..	10.10	..	..	15	20.20	..	..	..
r 16	..	..	8.8	..	..	r 16	15.18	..	..	..
17	..	..	..	..	..	17	40.40	..	..	..
18	..	..	..	..	..	18	..	10.12	..	..
19	..	12.15	..	..	..	19	..	..	..	15.18
r 20	..	5.10	..	..	..	20	40.60	..	..	..
21	..	..	..	..	..	21	20.25	..	..	..
22	..	..	10.15	..	..	r 22	25.30	..	..	..
23	..	..	20.20	..	..	r 23	30.35	..	..	..
24	..	Neg.	..	..	..	r 24	20.25	..	..	..
25	..	12.15	..	..	..	r 25	20.20 (40.40)	..	..	..
26	..	10.10	..	..	..	26	..	..	25.28	..
27	..	..	..	25.25	..	r 27	..	..	..	5.5
28	..	..	..	5.5	..	28	..	..	..	10.12
29	..	..	..	..	..	r 29	10.12	..	..	..
30	..	..	..	..	..	30	..	..	..	..
r 31	10.10	..	..	..	..	Respective totals...				
r 32	12.15	..	..	..	..	18	3	1	3	1
33	18.50	..	..	..	..	4				
r 34	..	..	..	..	..	The numbers underneath the biological columns, which indicate the results of the blood test, are the measurements in mm. of the tuberculin cutaneous test. A distinct halo to the cutaneous test is indicated by the numbers in parentheses. When the blood test could not definitely be put in either of two classifications, the measurements of the tuberculin reaction are put in both columns to indicate this. The letter r opposite the case number means that repeated observations have been made.				
35	..	..	..	..	..					
r 36	..	..	..	..	..	The numbers underneath the biological columns, which indicate the results of the blood test, are the measurements in mm. of the tuberculin cutaneous test. A distinct halo to the cutaneous test is indicated by the numbers in parentheses. When the blood test could not definitely be put in either of two classifications, the measurements of the tuberculin reaction are put in both columns to indicate this. The letter r opposite the case number means that repeated observations have been made.				
r 37	..	30.22	..	..	..					
r 38	5.5	..	..	..	..					
39	..	30.30	..	..	..					
r 40	5.5	..	..	..	..					
41	8.8	..	..	..	..					
42	..	..	..	..	..					
r 43	5.5	..	..	..	..					
r 44	..	15.15	..	..	..					
Respective totals.						13	4	12	2	6
						2	2	2	2	2

D. Results Obtained Upon Cases of Definite Pulmonary Tuberculosis.—It has been difficult to choose, from the various biological curves which have been obtained in this class, the few which would best illustrate the wide variety, their clinical correlation, and at the same time show the restrictions which must be remembered in a combined clinical and biological interpretation.

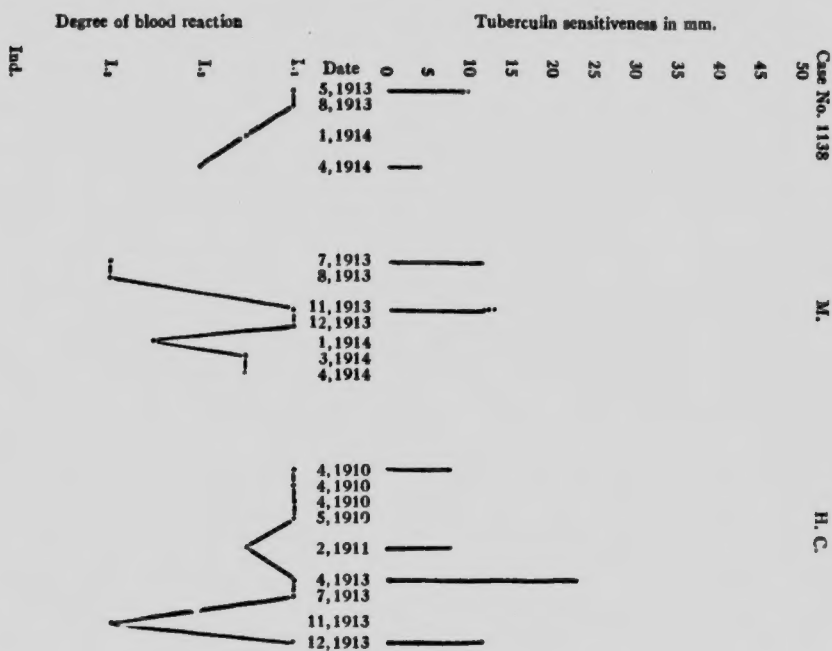


FIG. 2

In Case 1138 the initial observation was made during pregnancy; as previously the patient had been rapidly retrogressing, a Cæsarean section was under consideration. On account of the biological finding no interference was made and the case went to labor in November, 1913, with marked improvement. The slight drop subsequently may be the error of technic. The patient has remained in the better condition. Case M., a far-advanced involvement of both lungs, was running high fever at the time of the initial observations. Clinical improvement after the second observation was marked, locally and symptomatically. About the time of the fourth observation acute tuberculous laryngitis set in, which is apparently slowly improving. Case H. C., after returning from a sanatorium to work had an outbreak while not under observation in 1912. Since then he has done a full day's work in an office, with the one exception when he had a slight outbreak beginning about November, 1913, at which time tubercle bacilli were again obtained in the sputum. Is well and working at the present time. The change in the tuberculin sensitiveness before the outbreak is interesting.

The principal facts seem to be as follows:

(a) Increase of the inhibitive reactions precedes or accompanies favorable clinical progress; this is more marked the earlier the lesion, and seems more definite the more marked the tuberculin sensitiveness (or in a few cases the greater the tuberculin tolerance). Several instances of this are given in Fig. 2.

(b) Marked fixation, when sustained, is found in an entirely different type of case, which is nearly always febrile (Fig. 3).

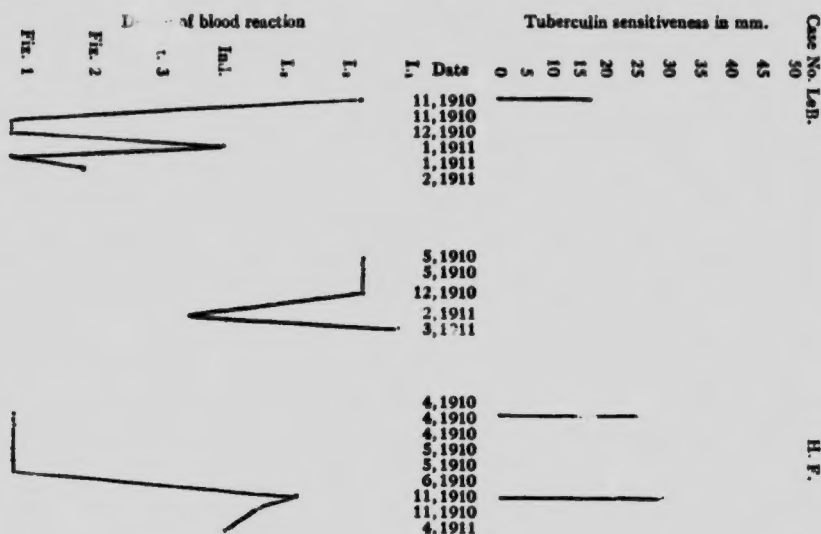


FIG. 3

These three cases represented in the beginning different amounts of anatomical involvement. All showed marked and rapid outbreaks of fever and retrogression from periods of comparative well-being. These outbreaks seemed to correspond with the blood results as accurately as the frequency of the tests allowed one to judge. Case H. F. J., acutely ill with temperature during part of 1910, improved considerably at the time the blood gave slight inhibitive reactions. Later, after a very marked retrogression during the summer of 1911, at which time the prognosis was apparently hopeless, a most dramatic recovery was made both focally and symptomatically. Unfortunately, tests could not be made at this time, so that it is only conjecture that he would have given a full inhibitive reaction, but consistent with daily findings with such a clinical picture.

(c) Sudden loss of inhibitive reaction or the development of fixation seems always to be accompanied by a clinical outbreak.

It is difficult to present percentage results regarding the correlation of these biological curves (specific to the tuberculous infection) with clinical variations, for such reasons as the difficulties of absolute diagnosis, the possible rôle of secondary infections, or any complication which makes the estimation of what is due solely to the tubercle bacillus an opinion rather than a fact. In certain far-advanced cases of ultimately hopeless prognosis we have obtained various degrees of the inhibitive phenomenon. Many of these cases have survived months longer than was at first deemed likely, or were apparently carried off by some complication. In none of these cases has the tuberculin sensitiveness been marked. However, nearly, if not all, the cases whose blood has been examined a short time before death have given the indifferent reaction.

E. Results Upon Other Forms of Tuberculous Infection.—Beyond a number

of cases of gland involvement, few observations have been made on the remaining types of tuberculous infection, sinus, bone, etc. Only one of the cases of tuberculous glands has given a complement fixation result; all the others have shown various degrees of the inhibitive phenomenon. There has been only one case of supposed tuberculosis of the peritoneum. This case was pronounced undoubtedly one of tuberculosis, even at the time of operation. From the degree of tuberculin sensitiveness and the extent of the inhibitive phenomenon, in consideration with the acuteness of the case, we did not consider that tuberculosis could be the cause of the clinical picture. Inoculation of a guinea-pig with the peritoneal exudate failed to cause tuberculosis. Shortly after the operation the autopsy revealed extensive carcinoma. A circular fibrosis in the intestinal wall, noticed at the time of the operation, was the chief cause for the surgical diagnosis; the postmortem revealed the lesions of healed tuberculosis.

SUMMARY

The facts as presented seem to give strong support to the following statements:

1. An initial tuberculous implantation, where successfully resisted, produces a marked ability of the serum to react with an alcohol-ether extract of tubercle bacilli, as is shown by loss of the power of the antigen-serum mixture to adsorb complement, i. e. contrast to this ability of a comparable antigen-salt mixture.
2. A reactivation or a reimplantation, when successfully resisted, results in an increase of the ability of the serum to react with antigen, but may not in all cases increase the tuberculin sensitiveness, which indeed in a few cases seems to be so slight that a negative von Pirquet skin test results with 10 c.c. of 50 per cent. old tuberculin.
3. Whatever phenomenon the reaction may represent, its estimation under certain restrictions is of practical value for certain cases in diagnosis, for others in prognosis, and in both it becomes an aid in treatment.

